Selective Inhibition of Matrix Metalloproteinase-9 Attenuates Traumatic Brain Injury-Mediated Blood-Brain Barrier Disruption in a Novel Dynamic in vitro Model

### Traumatic Brain Injuries
- Physical injury from an external force that causes impairment
- Inflammatory responses to primary injury amplify structural damage
- No reparative treatment—current methods have poor outcomes

### Blood-Brain Barrier
- **BBB Structure**
  - Endothelial cells, astrocytes, and pericytes
  - Cells have special characteristics that create restrictive permeability
  - Tight junctions enforce structural integrity
  - Matrix metalloproteinases maintain function

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#### Model Overview
- **Tri-culture** of human endothelial cells, astrocytes, and pericytes
- **Perfused** with continuously circulating media
- **Mimics** physiological conditions on the vascular and interstitial side
- **Real-time** and continuous measurements of barrier integrity, including TEER, hydraulic conductivity, and permeability assays
- Cells are continuously accessible for treatment variations

### Methods
- **Inhibition strategies**
  - Small interfering RNA
  - Synthetic inhibitor
  - Anti-MMP-9 antibody

### Results: Platform Metrics
- **Microvascular Barrier Integrity**
- **Hydraulic Conductivity**

### Results: Post-Analysis
- **Claudin-5 Western Blot**
- **MMP-9**
- **MMP-2**

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#### Discussion
- MMP-9 inhibition
- Restored barrier function
- Increased Claudin-5
- Antibody
- siRNA and inhibitor
- Only knocked-down MMP-9 expression
- Knocked-down MMP-9 and MMP-2 expression
- Least effective
- Significantly effective
- MMP-2 also plays a role in TBI-induced BBB hyperpermeability

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#### Future Directions
- Validate findings with additional trials in expanded model
- Model other barrier-modifying diseases
- Treatments preventing MMP-9 and MMP-2 upregulation
- Target MMPs in diseases beyond TBI